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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/856,282	DAVIS, BONNIE M	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,10-21,24-26 and 29-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,10-21,24-26 and 29-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 9/22/2008, are acknowledged and entered. Claims 1, 3-5, 10-21, 24-26, and 29-42 are pending and under examination.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 9/22/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 40 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding the trade names Probanthine and Robinul, is **withdrawn** in light of Applicant's amendments.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 10-21, 24-26, and 29-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the

claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to dosage forms comprising an effective amounts of a centrally-acting acetylcholinesterase inhibitor for the treatment of Alzheimer's disease wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined from four to twelve hours such that acetylcholinesterase inhibition is avoided during such a predetermined period and to methods of treating Alzheimer's disease comprising administering such a dosage form.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic dosage forms, *i.e.*, generic dosage forms comprising an effective amounts of a centrally-acting acetylcholinesterase inhibitor for the treatment of Alzheimer's disease.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species

encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

In the instant case, the claims contain functional language that fails to define what the claimed pharmaceutical compositions are made of. An example of such functional language is the following:

> "...wherein acetylcholinesterase inhibitor is formulated so as to delay its activity..." (claims 1 and 21).

In the above example, there is no description of what the pharmaceutical composition *contains* "so as to delay" the activity of the acetylcholinesterase inhibitor for a predetermined time period of from four to twelve hours as recited in the claims. For example, there are no excipients, sustained-release coatings, binders, surfactants, etc. recited in the claims or specification. As such, the claims lack written description because the claimed pharmaceutical compositions are not adequately described in a manner that would indicate what the compositions are composed of, other than the claimed acetylcholinesterase inhibitor(s).

The lack of written description of the instantly claimed compositions is further compounded by the fact that the compositions require specific delay periods of the active agents. It is noted that no specific formulations are disclosed in the specification and that Applicants have not described any specific examples of excipients, carriers, or extended release coatings that would result in the claimed delay periods of the active agents.

Aside from the very limited discussion provided in the specification, Applicants provide no direction as to (a) what excipients and extended release coatings out of all possible excipients and extended release coatings that exist in the art would have been reasonably expected to result in the claimed delay periods of the active agents and (b) which of those excipients and extended release coatings actually *do* result in the claimed delay periods of the active agents without having to execute hit or miss testing practices in order to make such a determination.

The need for testing amongst varying species and amounts of excipients and release coatings to determine what formulations would result in the claimed delay periods of the active agents demonstrates that Applicants were not in possession of the full scope of the compositions and methods now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure of specific active agents and preferable dosages, it remains that the claims recite a solely functional pharmaceutical composition. With the exception of the specific active agents recited in the claims, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other excipients, carriers, in-actives, and extended release coatings that may result in the claimed delay periods of the active agents, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention. It is also noted that the specification provides no examples of any particular compositions as recited in the instant claims.

Further, though Applicants have limited the claimed compositions to those that have particular delay periods of inactivity of the active agents, it remains that Applicants have not appropriately defined the metes and bounds of the claimed compositions, even when limited by function (step-plus-function form). As taught in the MPEP at § 2163, step-plus-function claims are not adequately described if "the written description adequately links or associates adequately described particular structure, material or acts to the function recited in a step-plus-function claim limitation," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application fails to meet these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function that would correlate a common structural element or material to performance of the claimed function and that would be readily identifiable to one of skill in the art.

Applicant's arguments have been carefully considered but they are not persuasive. As a first matter, Applicants state that "it seems strange" that this issue is being raised now for the first time. However, the Examiner respectfully submits that the actions of previous Examiners, while considered by the present Examiner, are not binding. Applicants assert that the specification at page 7 starting at line 20 states that formulations according to the invention can be obtained by use of the information set out in the text "Sustained Release Medications" by J.C. Johnson, Noyes Data Corporation 1980 or by the Conte reference cited in the present action in the context of a 35 U.S.C. 103 rejection. While dosage forms might certainly be prepared by the methods described in the aforementioned references, the fact remains that Applicants provide no direction as to (a) what excipients and extended release coatings out of all possible excipients and extended release coatings that exist in the art (including the excipients disclosed in the Johnson and Conte references) would have been reasonably expected to result in the claimed delay periods of the active agents and (b) which of those excipients and extended release coatings actually *do* result in the claimed delay periods of the active agents without having to execute hit or miss testing practices in order to make such a determination. Thus, while Applicants may have a plan for obtaining the claimed dosage forms, as discussed supra, *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. In the instant case, there is no evidence in the specification as filed that Applicants were in possession any dosage recited in the instant claims as evidenced by the complete lack of disclosure of a single pharmaceutical excipient or example of a dosage form of the invention.

Applicants argue that the nature and amount of suitable excipients for use in the present invention can readily be determined by those skilled in the art which Applicants assert is accepted by the Examiner since no issue is raised as to whether the present specification contains an enabling disclosure. The Examiner respectfully submits, however, that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115). As such, Applicant may very well have an enabling disclosure but lack written description and *vice versa*. The present issue is not whether one skilled in the art

could make the claimed dosage forms, but rather whether Applicant was in possession of the claimed dosage forms at the time the invention was made.

The Examiner respectfully disagrees with Applicant's characterization of the claimed invention wherein they state that we are not dealing with materials having unpredictable properties as in the University of Rochester case dealing with DNA. There are literally thousands of pharmaceutical excipients and coatings that might be applied to a pharmaceutical in order to delay its activity or provide sustained release. However, the claims require that the delay be from 4 to 12 hours and the specification does not disclose a single excipient, let alone an amount of a such an excipient, suitable for this purpose. Citing two references that broadly disclose sustained release medications and time-programmed release of drugs does not provide evidence that Applicants were in possession of the claimed dosage forms at the time the invention was made. Further, while the references were cited in the disclosure, there is no statement in the specification that the information contained therein is incorporated by reference into the disclosure.

Accordingly, the claims are deemed properly rejected as lacking written description for the claimed compositions and methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The instant claims recite dosage forms comprising a centrally-acting acetylcholinesterase inhibitor (*e.g.*, galanthamine) formulated so as to delay the activity of the acetylcholinesterase inhibitor for a predetermined period of from four to twelve hours.

Claims 1, 3-5, 10-19, 21, 24-26, and 29-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** (Published Nov. 17, 1988) in view of **Conte *et al***. (Biomaterials, 1993, vol. 14, no. 13, pages 1017-1023).

WO 88/08708 teaches compounds of formula (I) for use in the treatment of Alzheimer's disease (Abstract). Such compounds are galanthamine-analogues as recited in claims 1, 3-5, and 10-19 (pages 9-17). The compounds of the invention are inhibitors of acetylcholinesterase (page 38). Compositions for administration to patients having Alzheimer's disease, including sustained release delivery formulations, are taught at page 24, first and second paragraph. With respect to the claimed half life of from one to eleven hours as recited in the instant claims, the half life of any compound is a property of that compound and thus not separable from the compound itself. Therefore, because WO 88/08708 teaches the claimed compounds, the properties of these compounds that Applicants recite in the instant claims are necessarily present. WO 88/08708 does not teach a formulation wherein acetylcholinesterase inhibition is avoided for a predetermined period of from four to twelve hours as recited in the instant claims.

However, Conte *et al*. teach methods of formulating pharmaceutical active agents in press-coated tablets for time-programmed release of drugs (Abstract). The delay in release start is taught to not be influenced by the core composition and depends only on the shell formulation (*id*.). Suitable drugs for such time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (*e.g*., psychotropic active drugs) (page 1017, left column, second full paragraph). The press-coated tablets taught in Conte *et al*. release drugs at a specific rate, but the release starts only after a well defined period of time (page 1017, right column, first full paragraph). With respect to the delay periods recited in claims 1 and 3-4 (i.e., 4 to 12 hours, 6 to 9 hours, or 8 to 12 hours), Conte *et al*. teach such delay periods, *e.g*., 240 minutes, 480 minutes, and 720 minutes (Figures 6, 7, and 8).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate galanthamine or galanthamine-analogues as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al*. teach that psychotropic active drugs are agents having significant daily

variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity and thus suitable for incorporation into the press-coated tablets taught therein. In this regard, it is noted that WO 88/08708 teaches that galanthamine was known in the art as an agent useful in treating Alzheimer's disease "and related dementias" (page 1) and inhibits acetylcholinesterase (page 38), a reasonable interpretation of which is that galanthamine is a psychotropic drug and thus reasonably suggested by Conte *et al*.[1] Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping. As such, Conte *et al*. provides methods of formulating compositions that will aid in patient compliance, *i.e*., a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

Claims 1, 3-5, 20-21, 24-26 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Conte *et al***. in view of **Nordberg *et al.*** (Drug Safety, 1998, vol. 19, no. 6, pages 465-480) (newly cited – Abstract attached herein).

Conte *et al*. teach as discussed *supra*. The reference does not teach the acetylcholinesterase inhibitor, rivastigmine, as specifically recited in claims 20 and 38.

However, Nordberg *et al*. compare the tolerability and pharmacology of cholinesterase inhibitors in the treatment of Alzheimer's disease. In this regard, the reference teaches that cholinesterase inhibitors are currently the most established treatment strategy in Alzheimer's disease and that three cholinesterase inhibitors are in clinical use: tacrine, donepezil, and rivastigmine (Abstract). Further, Nordberg *et al*. teach that other cholinesterase inhibitors such as galanthamine (also recited in the instant claims) are under clinical evaluation (*id*.).

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate rivastigmine as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease.

[1] A psychotropic drug, as understood by those skilled in the art, is a chemical substance that acts primarily upon the

The skilled artisan would have been motivated to do so because Conte *et al*. teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity and thus suitable for incorporation into the press-coated tablets taught therein. In this regard, it is noted that Nordberg *et al*. teach that rivastigmine inhibits acetylcholinesterase and was known in the art as an agent useful in treating Alzheimer's disease (Abstract; pages 475-476), a reasonable interpretation of which is that rivastigmine is a psychotropic drug and thus reasonably suggested by Conte *et al*.[2] Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's dementia or behavioral abnormalities would not be in need of medication while they are sleeping. As such, Conte *et al*. provides methods of formulating compositions that will also aid in patient compliance, *i.e*., a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** and **Conte *et al***. as applied to claims 1, 3-5, 10-19, 21, 24-26, and 29-37 above, and further in view of **Faber *et al.*** (Am. J. Psychiatry, Jan. 1999, vol. 156, no. 1, page 156) (newly cited).

WO 88/08708 and Conte *et al*. teach as discussed *supra*. The references do not teach the administering of a compound (*e.g*., Probanthine) that reduces the peripheral effects of the claimed acetylcholinesterase inhibitors.

However, Faber *et al*. teach that propantheline[3], a peripherally acting anticholinergic medication, reduces the peripheral cholinergic activity caused by adminsitration of the cholinesterase inhibititor tacrine (page 156, left column). Based on the results of their study, the

central nervous system where it alters brain function.

[2] A psychotropic drug, as understood by those skilled in the art, is a chemical substance that acts primarily upon the central nervous system where it alters brain function.

[3] Propantheline is the common chemical name of the drug sold as Pro-Banthine.

authors suggest the use of adjunctive propantheline in patients with cholinergic effects from tacrine or other cholinesterase inhibitors.

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer acetylcholinesterase inhibitors as recited in the instant claims in conjunction with a compound that reduces its peripheral effects, such as propantheline as motivated and suggested by Faber *et al*.

Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** and **Conte *et al***. as applied to claims 1, 3-5, 10-19, 21, 24-26, and 29-37 above, and further in view of **Riemann et al.** (Psychiatry Research, 1994, vol. 51, pages 253-267).

This new rejection is necessitated by Applicant's submission of the IDS on 9/22/2008 which newly cites the Riemann et al. reference.

WO 88/08708 and Conte *et al*. teach as discussed *supra*. The references do not explicitly teach the administering of the formulations suggested therein so as to avoid release of the acetylcholinesterase inhibitor for the next anticipated sleep time (claim 41) or to allow a patient's central nervous system to become hypocholinergic during the period of desired sleep so as to avoid sleep disturbances during hours of desired sleep (claim 42).

However, firstly one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping. As such, Conte *et al*. provides methods of formulating compositions that will aid in patient compliance, *i.e.*, a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up. Riemann et al. teaches that galanthamine is used to treat Alzheimer's disease (page 254). In addition, Riemann et al. disclose that galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine (Table 3). Here, the skilled artisan is provided with the necessary motivation to develop controlled release formulations of galanthamine (such as those suggested and motivated by WO '708 in view of Conte *et al*.) in order to avoid waking a patient from sleep.

Accordingly, the skilled artisan would have been imbued with at least a reasonable expectation that delaying the release of galanthamine or analogues thereof during periods of sleep would avoid waking a patient from sleep since no anticholinesterase activity would occur. In support of this argument, the Examiner refers to Applicant's disclosure that it was known in the art at the time the invention was made that brain acetylcholine is elevated just before and during the time of activity, and reduced during sleep and that acetylcholinesterase activity, which keeps synaptic acetylcholine low, peaks during the subjective night, and is lowest during activity periods (citing Kametani, 1991; Mizuno, 1991; and Schiebeler, 1974). Applicants also acknowledge that it was known to those skilled in the art that systemic administration of the acetylcholinesterase inhibitors phsostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low disturb sleep and produce awakenings (citing Sitaram, 1979 and Reimann, 1994).

Response to Arguments

Applicant's arguments have been carefully considered but they are not persuasive. Firstly, Applicant argues that Conte does not use the phrase "psychotropic active drugs". Rather, Conte uses the phrase "...antiasthmatic, antihistaminic, psychotropic, anaesthetic, cardiovascular active drugs, NSAIDs, etc." Thus, Applicant asserts that Conte is referring to classes of drugs, not to properties which a drug might possess. The Examiner respectfully submits that Applicant is arguing semantics because Conte clearly suggests that essentially any drug can be incorporated into the dosage forms disclosed therein. As such, the fact that Conte does not explicitly recite "Alzheimer's drugs" is inconsequential to the present rejection. Applicant further argues that at the time of the Conte article, the term "psychotropic" was widely used as having a narrower meaning and "it seems" that Conte in fact meant when referring to "psychotropic" drugs to refer to such conventional psychotropic drugs. This is not persuasive because Applicant could not have known what Conte meant by psychotropic drug. The fact that the PDR dose not list Alzheimer drugs as psychotropic drugs does not mean that Alzheimer drugs would not fall under this broad category of drugs. In fact, the PDR lists antianxiety agents, hypnotics, mood stabilizers, antipsychotic, and antidepressant drugs, all of which acts primarily on the CNS to

alter brain function. One skilled in the art would clearly recognize that anticholinergic drugs such as the Alzheimer drugs disclsoed in WO '708 would fall in this category. In fact, as acknowledged by Applicant, Cummings notes that "Cholinergic compounds are unique **psychotropic agents**....". Accordingly, Applicant's argument that there is no reason why one skilled in the art would have combined Conte and WO 88/108708 is not found persuasive.

Secondly, Applicant argues that the Examiner's statement that one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's disease or other dementia would not be in need of medication while they are sleeping is incorrect. In support of this argument, Applicant cites several articles purported to teach that the art preferred a continuously-acting cholinesterase inhibitor to one which worked only during the day. However, Applicant also discloses that it was known to those skilled in the art that brain acetylcholine is elevated just before and during the time of activity, and reduced during sleep and that acetylcholinesterase activity, which keeps synaptic acetylcholine low, peaks during the subjective night, and is lowest during activity periods (citing Kametani, 1991; Mizuno, 1991; and Schiebeler, 1974). Applicants also acknowledge that it was known to those skilled in the art that systemic administration of the acetylcholinesterase inhibitors phsostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low disturb sleep and produce awakenings (citing Sitaram, 1979 and Reimann, 1994). As such, one skilled in the art would clearly recognize the benefit of delayed release of an acetylcholinesterase inhibitor taking before bedtime. The fact that 24-hour versus daytime treatment of Alzheimer's disease might be "preferred" does not negate the obvious benefit that would be expected from the dosage forms suggested by the cited prior art. Further, Applicant's argument that there is "even today" no recognition of the inadvisability of inhibiting acetylcholinesterase during the night is negated by the fact that galantamine was produced in an awaketime-only formulation after the submission of the present application.

Thirdly, Applicant discusses an aspect of the present invention wherein the claimed formualtions are used to normalize the circadian rhythm itself (e.g., claim 42). However, claim 42 is a method of treating Alzheimer's disease comprising administering to an Alzheimer's disease patient a composition comprising a centrally-acting acetyl cholinesterase inhibitor wherein the nature of the composition and the time of administration of the inhibitor from the

composition "is such as to" minimize release prior and during to desired sleep hours. This is an effect of the compositions and methods taught, suggested, and motivated by the cited prior art and is thus not a patentable distinction over the prior art. In response to applicant's argument that the prior art does not teach the notion of giving a drug to alter the circadian rhythm itself, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Applicant's discussion of the prior at pages 16-19 of their response all relate to circadian rhythms in Alzheimer's disease and will not be addressed by the Examiner in detail.

Fourthly, Applicant appears to be arguing unexpected results at pages 19-23 of the response. The Examiner has carefully considered Applicant's argument but it is not clear what unexpected result Applicant is claiming. Applicant refers to published studies and copies figures from some of these publications but nowhere is evidence provided that a composition *as claimed* was tested and compared to a *different* composition of the claimed acetylcholinesterase inhibitors. As such, no evidence of an unexpected result resulting from the claimed compositions has been proffered.

Fifthly, regarding the Moorman reference, Applicant argues that the twilight sleep referred to in Moorman is not normal sleep. In view of Applicant's arguments and the IDS filed 9/22/2008, the Examiner is removing the Moorman reference and replacing it with Reimann et al. (newly cited by Applicants). Conte and WO '708 teach, suggest, and motivate one skilled in the art to administer the claimed compositions to patients with Alzheimer's disease and one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's or other dementia would not be in need of medication while they are sleeping. As such, Conte *et al.* provides methods of formulating compositions that will aid in patient compliance, *i.e.*, a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up. Riemann et al. disclose that galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine (Table 3). As such, the skilled artisan would recognize the benefit of

administering a dosage form of galanthamine that can be administered before sleep but avoids release of the drug while a patient is sleeping so as to not disturb normal sleep patterns.

Accordingly, the rejections are deemed proper and are maintained for the reasons of record and as reiterated above.

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 9/22/2008 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614